

## CLAIMS

1. A method to produce a human immunoglobulin or an analog thereof, specific for a desired antigen, which method comprises:

administering said antigen or an immunogenic portion thereof to a nonhuman animal under conditions to stimulate an immune response, whereby said animal produces B cells that secrete immunoglobulin specific for said antigen; wherein said nonhuman animal is characterized by being substantially incapable of producing endogenous heavy and light immunoglobulin chains, but capable of producing human immunoglobulin; and

recovering said immunoglobulin or analog.

2. The method of claim 1 wherein said recovering step comprises recovering polyclonal immunoglobulin or analog from said animal.

3. The method of claim 1 wherein said recovering step comprises immortalizing B cells from said animal immunized with said antigen, screening the resulting immortalized cells for the secretion of said immunoglobulin specific for said antigen, and

a) recovering immunoglobulin secreted by said immortalized B cells, or

b) recovering the genes encoding at least the immunoglobulin from the immortalized B cells, and optionally modifying said genes;

expressing said genes or modified forms thereof to produce immunoglobulin or analog; and

recovering said immunoglobulin or analog.

4. The method of claim 1 wherein said recovering step comprises:

recovering genes encoding the immunoglobulins from the primary B cells of the animal;

generating a library of said genes expressing the immunoglobulins;

screening the library for an immunoglobulin with the desired affinity for the antigen;

recovering the genes encoding the immunoglobulin; expressing said recovered genes to produce an immunoglobulin or analog recovering said immunoglobulin or analog.

5. A recombinant DNA molecule comprising a nucleotide sequence encoding the immunoglobulin or analog produced by the method of claim 1.

6. The DNA molecule of claim 5 wherein said encoding-nucleotide sequence is operably linked to control sequences capable of effecting its expression.

7. A cell or cell line modified to contain the DNA molecule of claim 6.

8. A method to produce a fully human immunoglobulin or an analog thereof which method comprises culturing the cells of claim 7 under conditions whereby said encoding nucleotide sequence is expressed to produce said immunoglobulin or analog; and recovering said immunoglobulin or analog.

9. A DNA molecule comprising a nucleotide sequence corresponding to the gene or modified gene prepared by the method of claim 3.

10. The DNA molecule of claim 9 wherein said encoding nucleotide sequence is operably linked to control sequences capable of effecting its expression.

11. A cell or cell line modified to contain the DNA molecule of claim 9.

12. A method to produce a fully human immunoglobulin or an analog thereof which method comprises culturing the cells of claim 11 under conditions whereby said encoding nucleotide sequence is expressed to produce said immunoglobulin or analog; and recovering said immunoglobulin or analog.

13. A DNA molecule which comprises a nucleotide sequence encoding a human immunoglobulin with desired affinity prepared according to the method of claim 4.

14. The DNA molecule of claim 13 wherein said encoding nucleotide sequence is operably linked to control sequences capable of effecting its expression.

15. A cell or cell line modified to contain the DNA molecule of claim 13.

16. A method to produce a fully human immunoglobulin or an analog thereof which method comprises culturing the cells of claim 15 under conditions whereby said encoding nucleotide sequence is expressed to produce said immunoglobulin or analog; and recovering said immunoglobulin or analog.

17. An immortalized B cell which secretes a fully human immunoglobulin to a desired antigen prepared according to claim 3.

18. A method to produce an immunoglobulin or analog which comprises culturing the cells of claim 17 and recovering said immunoglobulin or analog.

19. A fully human immunoglobulin or analog produced by the method of claim 1.

20. The immunoglobulin or analog of claim 19 wherein the desired antigen is selected from the group consisting of

the leukocyte markers, CD2, CD3, CD4, CD5, CD6, CD7, CD8, CD11a,b,c, CD13, CD14, CD18, CD19, CD20, CD22, CD23, CD27 and its ligand, CD28 and its ligands B7.1, B7.2, B7.3, CD29 and its ligand, CD30 and its ligand, CD40 and its ligand gp39, CD44, CD45 and isoforms, CDw52 (Campath antigen), CD56, CD58, CD69, CD72, CTLA-4, LFA-1 and TCR;

the histocompatibility antigens, MHC class I or II, the Lewis Y antigens, SLe<sup>x</sup>, SLe<sup>y</sup>, SLe<sup>a</sup>, and SLe<sup>b</sup>;

the integrins, VLA-1, VLA-2, VLA-3, VLA-4, VLA-5, VLA-6,  $\alpha$ V $\beta$ 3, and LFA-1, Mac-1, and p150,95,  $\alpha$ <sub>v</sub> $\beta$ <sub>1</sub>, gpIIbIIIa,  $\alpha$ <sub>R</sub> $\beta$ <sub>3</sub>,  $\alpha$ <sub>6</sub> $\beta$ <sub>4</sub>,  $\alpha$ <sub>v</sub> $\beta$ <sub>5</sub>,  $\alpha$ <sub>v</sub> $\beta$ <sub>6</sub>, and  $\alpha$ <sub>v</sub> $\beta$ <sub>7</sub>;

the selectins, L-selectin, P-selectin, and E-selectin and their counterreceptors VCAM-1, ICAM-1, ICAM-2, and LFA-3;

the interleukins, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, and IL-15;

the interleukin receptor is selected from the group consisting of IL-1R, IL-2R, IL-3R, IL-4R, IL-5R, IL-6R, IL-7R, IL-8R, IL-9R, IL-10R, IL-11R, IL-12R, IL-13R, IL-14R, and IL-15R;

the chemokine is selected from the group consisting of PF4, RANTES, MIP1 $\alpha$ , MCP1, NAP-2, Gro $\alpha$ , Gro $\beta$ , and IL-8;

the growth factor is selected from the group consisting of TNF $\alpha$ , TGF $\beta$ , TSH, VEGF/VPF, PTHrP, EGF family, FGF, PDGF family, endothelin, Fibronectin (F<sub>s</sub>F<sub>1</sub>), human Laminin, and gastrin releasing peptide (GRP);

the growth factor receptor is selected from the group consisting of TNF $\alpha$ R, TGF $\beta$ R, TSHR, VEGFR/VPFR, FGFR, EGFR, PTHrPR, PDGFR family, EPO-R, G-CSF-R and other hematopoietic receptors;

the interferon receptor is selected from the group consisting of IFN $\alpha$ R, IFN $\beta$ R, and IFN $\lambda$ R;

the Ig and its receptor is selected from the group consisting of IgE, Fc $\epsilon$ R1, and Fc $\epsilon$ R2;

the tumor antigen is selected from the group consisting of her2-neu, mucin, CEA and endosialin;

the allergen is selected from the group consisting of house dust mite antigen, lol p1 (grass) antigens, and urushiol;

the viral protein is selected from the group consisting of CMV glycoproteins B, H, and gCIII, HIV-1 envelope glycoproteins, RSV envelope glycoproteins, HSV envelope glycoproteins, HPV envelope glycoproteins, Hepatitis family surface antigens;

the toxin is selected from the group consisting of pseudomonas endotoxin and osteopontin/uropontin, snake venom, spider venom, and bee venom conotoxin;

the blood factor is selected from the group consisting of complement C3b, complement C4a, complement C4b-9, Rh factor, fibrinogen, fibrin, and myelin associated growth inhibitor; and

the enzyme is selected from the group consisting of cholesterol ester transfer protein, membrane bound matrix metalloproteases, and glutamic acid decarboxylase (GAD).

21. The immunoglobulin or analog of claim 14 wherein said desired antigen is selected from the group consisting of human IL-6, human IL-8, human TNF $\alpha$ , human CD4, human L-selectin, human gp39, human IgE, human  $\alpha$ V $\beta$ 3, human Fibrosin (F<sub>s</sub>F<sub>1</sub>), human laminin, human PTHrp, and tetanus toxin C(TTC).

22. A recombinant DNA molecule comprising a nucleotide sequence that encodes the immunoglobulin or analog of claim 19-21.

23. The DNA molecule of claim 22 wherein said encoding nucleotide sequence is preferably linked to control sequences capable of effecting its expression.

24. A cell or cell line modified to contain the DNA molecule of claim 23.

25. A method to produce an immunoglobulin or analog specific for a desired antigen which method comprises culturing the cell or cell line of claim 24 under conditions wherein said nucleotide sequence is expressed to produce said immunoglobulin or analog; and recovering the immunoglobulin or analog.

26. An human antibody or analog thereof which is specifically immunoreactive with an antigen selected from the group consisting of transition state mimics; leukocyte markers; histocompatibility antigens; adhesion molecules; interleukins; interleukin receptors; chemokines; growth factors; growth factor receptors; interferon receptors; Igs and their receptors, tumor antigens; allergens; viral proteins; toxins; blood factors; enzymes; and the miscellaneous antigens ganglioside GD3, ganglioside GB2, LMP1, LMP2, eosinophil major basic protein, eosinophil cationic protein, pANCA, Amadori protein, Type IV collagen, glycosylated lipids,  $\lambda$ -interferon, A7, P-glycoprotein, Fas (AFO-1) and oxidized-LDL.

27. The antibody or analog of claim 26 wherein the leukocyte marker is selected from the group consisting of CD2, CD3, CD4, CD5, CD6, CD7, CD8, CD11a,b,c, CD13, CD14, CD18, CD19, CD20, CD22, CD23, CD27 and its ligand, CD28 and its ligands B7.1, B7.2, B7.3, CD29 and its ligand, CD30 and its ligand, CD40 and its ligand gp39, CD44, CD45 and isoforms, CDw52 (Campath antigen), CD56, CD58, CD69, CD72, CTLA-4, LFA-1 and TCR;

the histocompatibility antigen is selected from the group consisting of MHC class I or II, the Lewis y antigens, SLex, SLey, Slea, and SLeb;

the adhesion molecule is selected from the group consisting of VLA-1, VLA-2, VLA-3, VLA-4, VLA-5, VLA-6,  $\alpha_V\beta_3$ , and LFA-1, Mac-1, p150,95,  $\alpha_V\beta_1$ , gpIIbIIIa,  $\alpha_R\beta_3$ ,  $\alpha_6\beta_4$ ,  $\alpha_V\beta_5$ ,  $\alpha_V\beta_6$ , and  $\alpha_V\beta_7$ , L-selectin, P-selectin, and E-selectin and their counterreceptors VCAM-1, ICAM-1, ICAM-2, and LFA-3;

the interleukin is selected from the group consisting of IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, ad IL-15;

the interleukin receptor is selected from the group consisting of IL-1R, IL-2R, IL-3R, IL-4R, IL-5R, IL-6R, IL-7R, IL-8R, IL-9R, IL-10R, IL-11R, IL-12R, IL-13R, IL-14R, and IL-15R,

the chemokine is selected from the group consisting of PF4, RANTES, MIP1 $\alpha$ , MCP1, NAP-2, Gro $\alpha$ , Gro $\beta$ , and IL-8;

the growth factor is selected from the group consisting of TNF $\alpha$ , TGF $\beta$ , TSH, VEGF/VPF, PthrP, EGF family, FGF, PDGF family, endothelia, Fibrosin (F $_s$ F $_{-1}$ ), human Laminin, and gastrin releasing peptide (GRP);

the growth factor receptor is selected from the group consisting of TNF $\alpha$ R, RGF $\beta$ R, TSHR, VEGFR/VPFR, FGFR, EGFR, PTHrPR, PDGFR family, EPO-R, GCSF-R and other hematopoietic receptors;

the interferon receptor is selected from the group consisting of IFN $\alpha$ R, IFN $\beta$ R, and IFN $\gamma$ R;

the Ig and its receptor is selected from the group IgE, Fc $\epsilon$ RI, and Fc $\epsilon$ RII;

tumor antigen is selected from the group her2-neu, mucin, CEA and endosialin;

the allergen is selected from the group consisting of house dust mite antigen, lol pl (grass) antigens, and urushiol;

the viral protein is selected from the group consisting of CVM glycoproteins B, H, and GCIII, HIV-1 envelope glycoproteins, RSV envelope glycoproteins, HSV envelope glycoproteins, EBV envelope glycoproteins, VZV envelope glycoproteins, HPV envelope glycoproteins, Hepatitis family surface antigens;

the toxin is selected form the group consisting of pseudomonas endotoxin and osteopontin/uropontin, snake venom, and bee venom;

the blood factor is selected from the group consisting of complement C3b, complement C5a, complement C5b-

9, RH factor, fibrinogen, fibrin, and myelin associated growth inhibitor; and

The enzyme is selected from the group consisting of cholesterol ester transfer protein, membrane bound matrix metalloproteases, and glutamic acid decarboxylase (GAD)

28. The antibody or analog of claim 26 wherein the desired antigen is selected from the group consisting of human IL-6, human IL-8, human TNF $\alpha$ , human CD4, human L-selectin, human gp39, human IgE and tetanus toxin C (TTC).

29. The antibody or analog of claim 19 wherein the desired antigen is human IL-6.

30. The antibody or analog of claim 19 wherein the described antigen is human IL-8.

31. The antibody or analog of claim 19 wherein the desired antigen is human TNF $\alpha$ .

32. The antibody or analog of claim 19 wherein the desired antigen is human CD4.

33. The antibody or analog of claim 19 wherein the desired antigen is human L-selectin.

34. The antibody or analog of claim 19 wherein the desired antigen is human gp39.

35. The antibody or analog of claim 19 wherein the desired antigen is tetanus toxin C (TTC).

36. The antibody or analog of claim 19 wherein the desired antigen is human IgE.

37. The antibody or analog of claim 19 wherein the desired antigen is human  $\alpha V\beta 3$ .



38. The antibody or analog of claim 19 wherein the desired antigen is human fibrosin.

5 39. The antibody or analog of claim 19 wherein the desired antigen is human PTHrp.

40. The antibody or analog of claim 26 which is an agonist or is a catalyst.

10 41. A recombinant DNA molecule encoding the antibody of any of claim 26-40.

15 42. A recombinant DNA molecule which comprises an expression system for the antibody or analog of any claims 26-40 which expression system comprises a nucleotide sequence encoding said antibody or analog operably linked to control sequences capable of effecting its expression.

20 43. A recombinant host cell which is modified to contain the DNA molecule of claim 42.

25 44. A method to produce an antibody or analog which method comprises culturing cells of claim 43 under conditions wherein said coding sequence is expressed; and recovery the antibody of analog produced.

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